REMARKS

Reconsideration and withdrawal of the rejections of the present application are respectfully requested in view of the remarks presented herewith, which place the application into condition for allowance.

Status of the Claims and Formal Matters

Claims 1-45 are pending. Per the Examiner's election / restriction requirement, claims 1, 2, 4-15, and 20-22 are currently being prosecuted in this case and have been examined on the merits. Claims 3, 16-19 and 23-45 are withdrawn from further consideration pursuant to 37 CFR 1.142(b).

35 U.S.C. §112, First Paragraph – Enablement

Claims 1, 2, 4-15 and 20-22 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement (Office Action, pages 4-8). The Examiner states that the claims contain subject matter which was allegedly not described in the specification in such a way as to enable one of skill in the art to make or use the claimed invention. Applicants respectfully traverse this rejection.

The test for enablement is whether one reasonably skilled in the art could make or use the claimed invention without undue experimentation, based on the disclosure in the application and the information available in the art. *United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988); MPEP § 2164.01. The Office must consider many factors for enablement, including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art,

the relative skill of those in that art, the predictability or unpredictability of the art, and the breadth of the claims. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988); MPEP § 2164.01(a).

Applicants respectfully point to the significant guidance and working examples provided in the instant case. Thus, the instant application demonstrates, *inter alia,* and in Example 41, Tables 3 and 4, at page 35-37 of the specification as filed, the efficacy of the claimed compounds to inhibit orthopox viral induced cytophathic effect (CPE). For these experiments, the CPE-based assay was used to evaluate the ability of the claimed compounds to inhibit orthopoxvirus-induced CPE. As shown in Table 3, instant compounds are excellent inhibitors of orthopox viral induced cytophathic effect as demonstrated by low EC50 values <0.5μM (compared to EC50 values > 50μM obtained for inhibition of unrelated viruses). Further, the claimed compounds exhibited anti-viral potency and selectivity at concentrations non-toxic to the cells as determined by MTT assays.

Further, the Examiner is respectfully directed to Exhibit 1, (Yang et al., Journal of Virology, Oct. 2005, pages 13139-13149), wherein authors , which include an instant inventor Robert Jordan, submit evidence of the *vivo* efficacy of claimed compounds to inhibit extracellular virus formation and treat and prevent lethal orthopoxvirus challenge in mice. Thus, Exhibit 1 provides in *vivo* efficacy data for a representative claimed compound ST-246, 4-Trifluromethyl-N-(3, 3a, 4, 4a, 5, 5a, 6, 6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1h)-yl)benzamide, see Table 1, Example Number 1 at page 24 of the instant specification. To demonstrate in *vivo* efficacy, the claimed compound ST-246 was orally administered to mice at 100mg/kg of body weight/day for 14 days, was well tolerated and resulted in reduction of viral titers and protection against virus-induced disease. Specifically, as shown in Table 3 and Figure 7 of Exhibit 1, oral administration of ST-246 protected mice from challenge with ectromelia

virus, a natural orthopoxvirus of laboratory mice that causes a generalized disease mousepox, *inter alia*, by reducing viral titers in lung, liver and spleens of infected mice by at least 5 orders of magnitude relative to placebo-treated mice. The authors further note that ST-246 targets the virulence factor without diminishing development of protective immunity of the host. Thus, mice that survive the infection as a result of ST-246 treatment were immune to the future challenges with a lethal dose of the virus. In sum, these studies unequivocally demonstrate that claimed compounds are potent and specific inhibitors of orthopoxvirus replication and infection in *vivo*.

Applicant's next point to the state of the art at the time of filing. One skilled in the art of virology is aware that viral replication can be monitored *inter alia* by cytopathic effect (CPE) observation, electron microscopy, RT-PCR and other well known methods in the art, which are for example described in Fields Virology, Chapter 2, volume 1 4th addition. 2001, Editors Knipe, D.M., and Howley, P.M. The CPE assay is an extension of the plaque assay, developed to study bacteriophage (viruses that infect bacteria) and adapted by Dulbecco to animal viruses in 1953 (See Exhibit 2, Dublecco R., and Vogt, M., Cold Spring Harb Symp Quant Biol, 1953; 18. Pp273-279.). Since CPE is directly related to viral replication, compounds that inhibit viral replication in cell culture can be identified readily as conferring protection from virus-induced CPE (see Exhibit 3, Schmidtke et al. 2001). The knowledge of those skilled in the art are replete with examples of the use of CPE assays to identify potent and selective viral inhibitors, see Exhibit 1, and also Exhibit 4 (Quenelle et al., Antiviral Research 63, pages 33-40, 2004). Thus, both Exhibits demonstrate the feasibility of the CPE assay to correctly identify a potent and selective viral inhibitor in *vitro* before successfully testing the identified compound in *vivo*. It is important to note, that as stated at page 5 of the instant specification and noted by the Examiner

(Office Action, at page 5), it is theoretically possible to inhibit CPE without inhibiting virus replication. The case for this type of viral replication- independent CPE is not yet clearly understood but exists and possibly relates to early induction of cell rounding and cell death (see Exhibit 5, Tsung, et al., Journal of Virology, Vol. 70, page 165-171). In sum, the state of the art is replete with examples supporting the feasibility of CPE assay for testing and identification of novel selective inhibitors of orthopoxviral infections which demonstrate potency and selectivity in *vitro* and further anti-viral efficacy in *vivo*.

Notably, the test for "undue experimentation" is not merely quantitative, and the time and difficulty experimentation are not determinative. *Wands*, 858 F.2d at 737; MPEP § 2164.06. A considerable amount of experimentation is permissible if it is merely routine or if the specification provides a reasonable amount of guidance for how the experimentation should proceed. *Wands*, 858 F.2d at 737; MPEP § 2164.06. Where an invention involves biological activity, this itself does not constitute "undue experimentation," particularly where the level of skill is high (as noted in the instant case; *see* Office Action, page 6-7). *Wands*, 858 F.2d at 740. Furthermore, Applicants need only provide *sufficient* disclosure to teach those of skill in the art how to make and use the claimed invention. MPEP § 2164. The standard does not require thousands of examples or every possible species for the claimed invention. *In re Angstadt*, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976).

Thus, the instant application provides considerable guidance and working examples for use of claimed compounds for treating and prevention of orthopoxviral infection. Furthermore, the state of the art has provided known techniques for testing the efficacy of the claimed compounds both in *vivo* and in *vitro*. Therefore, taken together, at the time of filing, one of skill in the art would be able to make, test and use the claimed compounds without undue

experimentation to treat and prevent orthopoxvirus infections and associated diseases. Thus, Applicants urge that the specification provides sufficient enablement for the claimed methods and respectfully request withdrawal of this rejection.

Applicants respectfully submit that its pending claims are in condition for allowance. If there are any additional fees, the Director is authorized to charge any deficiency, or credit any overpayment, to our Deposit Account No. 50-0540.

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